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In 09/485,598

Part 9 #16

NOTARIAL CERTIFICATE

CANADA)
)
PROVINCE OF ONTARIO)
)
TO WIT:)

TO ALL WHOM THESE PRESENTS MAY COME, BE SEEN OR KNOWN

I, NEIL H. HUGHES, a Notary Public, in and for the Province of Ontario, by Royal Authority duly appointed, residing in the City of Mississauga, in the Regional Municipality of Peel in said Province, DO CERTIFY AND ATTEST that the paper-writing hereto annexed is a true copy of a document produced and shown to me and purporting to be the **Declaration of Dr. Robert Samuel Langer sworn on the 5th day of November, 2002 attaching Exhibits A and B**, the said copy having been compared by me with the said original document, an act whereof being requested I have granted under my Notarial Form and Seal of Office to serve and avail as occasion shall or may require.

IN TESTIMONY WHEREOF I have hereto subscribed my name and affixed my Notarial Seal of Office at the Town of Markham, in the Regional Municipality of York, this 6th day of November, 2002.

A Notary Public in and for the Province of Ontario

NEIL HARVEY HUGHES, Notary Public, Province of Ontario, limited to the attestation of instruments and the taking of affidavits, for Ivor M. Hughes, Barrister and Solicitor, Patent & Trademark Agents. Expires March 30, 2004.

IN THE MATTER OF UNITED STATES PATENT APPLICATION SERIAL NO. **09/485,598** PHARMACEUTICAL COMPOSITIONS COMPRISING CEFUROXIME AXETIL OF **BERNARD CHARLES SHERMAN**, APPLICANT AND THE INVENTOR OF THE SUBJECT MATTER THEREIN.

DECLARATION

I, DR. ROBERT SAMUEL LANGER, of the City of CAMBRIDGE, in the State of MASSACHUSETTS, MAKE OATH AND SAY AS FOLLOWS:

1. I am currently the Kenneth J. Germeshausen Professor of Chemical and Biomedical Engineering at MIT, Department of Chemical Engineering, Whitaker College of Health Sciences, Technology and Management and the Harvard-MIT Division of Health Sciences and Technology. The professional positions which I have held, the various publications of which I am the author or co-author, and other details of my professional qualifications including awards I have received, scientific advisory boards and editorial boards of which I am a member, are set out in my *curriculum vitae*, which is attached hereto and marked as **Exhibit A** to this my second Declaration concerning this matter. As a result, I consider myself an expert with respect to pharmaceutics, controlled release technology and delivery systems for drugs.

2. I previously submitted a Declaration concerning this matter that contained my comments and opinions concerning the various compositions claimed in U.S. Patent

Application No. 09/485,598 entitled "Pharmaceutical Compositions Comprising Cefuroxime Axetil".

3. For my previous Declaration, I was asked by Neil H. Hughes, Patent Agent of the firm Ivor M. Hughes Barristers and Solicitors, Patent and Trade Mark Agents, Counsel for the inventor Dr. Bernard Charles Sherman, to provide my opinion concerning the position taken by the United States Patent Office Examiner and her rejection of the aforementioned claims and amended claims of U.S. Patent Application No. 09/485,598 (the '598 patent application). In particular, I was asked to provide my opinion with respect to the U.S. Examiner's allegation that compositions disclosed as described in claims 1 and 15 listed above were allegedly obvious in light of the following two U.S. Patents: (i) U.S. Patent No. 5,776,495 (the '495 patent, assigned to Duclos et al.) and (ii) U.S. Patent No. 4,820,833 (the '833 patent, assigned to Crisp et al.). I was also asked to provide my comments concerning the decision for granting an interim restraining order and injunction.

4. To summarize, in my previous Declaration I stated my opinion that the teachings of the '495 and '833 patents, considered alone or in any combination, do not render obvious the claims in question of the '598 patent application, namely, novel co-precipitate compositions containing cefuroxime axetil that possess optimized properties with respect to their dissolution behavior.

5. In paragraphs 22 through 33 of my previous Declaration, I stated in part my opinion that the amorphous coprecipitates of cefuroxime axetil and excipients such as sorbitol and zinc chloride produced via spray-drying as described in the '598 patent application and copending application serial N. 09/621,676 (the '676 application) are distinct and different from the highly pure, substantially amorphous forms of cefuroxime axetil produced via spray-drying as described in the '833 patent. In particular, I stated in my previous Declaration that it is my opinion that the teachings of the '833 patent toward the production of **highly pure**, substantially amorphous forms of cefuróxime axetil do not make obvious nor teach towards the production of **non-pure**, amorphous dispersions of cefuroxime axetil and excipients such as sorbitol and zinc chloride as described in the '598 and '676 patent applications.

6. To further support my opinions with respect to this matter, I was asked by Counsel for Apotex Inc. to conduct experiments that would demonstrate the fact that amorphous coprecipitates or dispersions of cefuroxime axetil and excipients such as sorbitol and zinc chloride produced via spray-drying as described in the '598 and '676 patent applications are distinct and different from the highly pure, substantially amorphous forms of cefuroxime axetil produced via spray-drying as described in the '833 patent.

7. In my opinion, one straightforward way to clearly demonstrate this fact experimentally is to measure and compare the glass transition temperatures of amorphous materials comprising or containing cefuroxime axetil based on the teachings of the '833

patent and the '598 and '676 patent applications. The '833 patent teaches the spray-drying of highly pure cefuroxime axetil from various solvent systems. No teachings are provided within the '833 patent with respect to the introduction of any other solids or excipients for the purposes of co-spray-drying with cefuroxime axetil. Thus, unless there are appreciable amounts of residual spray-drying solvent present, one would expect the properties of the amorphous phases taught for production via spray-drying in the '833 patent to be those of a highly pure, substantially amorphous form of cefuroxime axetil, which is what is indeed claimed in the '833 patent.

8. In contrast, the '598 and '676 patent applications teach the co-spray-drying of cefuroxime axetil with excipients such as sorbitol and zinc chloride. For the purposes of this Declaration, I have chosen two compositions taught in the '598 and '676 patent applications as representative examples (designated as Apotex 1 and Apotex 2):

(i) 91:9 wt%:wt% cefuroxime axetil:sorbitol (Apotex 1)

(ii) 90:9:1 wt%:wt%:wt% cefuroxime axetil:sorbitol:zinc chloride (Apotex 2)

As I stated in my previous Declaration, in my opinion, these compositions upon spray-drying are clearly not highly pure, substantially amorphous forms of cefuroxime axetil. With respect to the properties of Apotex 1, as I described in my previous Declaration, sorbitol in amounts such as those listed in the Apotex 1 composition (9 wt%) is known to act upon inclusion in certain amorphous materials as a plasticizer, lowering the glass transition temperature and thus changing the properties of the resultant amorphous phase.

It is also known that such a plasticization effect is the result of an interaction and intermixing of the plasticizer with the additional amorphous material on a molecular level. With respect to the properties of Apotex 2 which also contains 1 wt% zinc chloride, zinc chloride on its own is not known to possess the propensity to form an amorphous phase. However, it is known that metal counterions can have an influence on the glass transition properties of amorphous phase materials in some cases.

9. Thus, in my opinion, measuring the glass transition temperatures of the amorphous phases comprising or containing cefuroxime axetil as taught in the '833 patent (case A) and '598 and '676 patent applications (case B) allows for a straightforward determination of whether or not a given amorphous phase can be defined as a **highly pure**, substantially amorphous phase of cefuroxime axetil. For case A, a highly pure, substantially amorphous form of cefuroxime axetil, produced via the spray-drying of cefuroxime axetil dissolved in a given solvent utilizing a given spray-drier and set of spray-drying conditions should result in the production of an amorphous material with a defined glass transition temperature, such a process is taught in the '833 patent. For case B, if the inclusion of excipients such as sorbitol and zinc chloride in the spray-drying solvent in addition to cefuroxime axetil results in the production of an amorphous phase with a different glass transition temperature than seen for case A, in my opinion, such an amorphous phase would not be defined as a highly pure, substantially amorphous form of cefuroxime axetil.

10. To investigate this, I asked three researchers from my laboratory group, these being Dr. Daniel Anderson (post-doctoral student), Dr. Daniel Kohane (research affiliate) and Amy Grayson (graduate student) to utilize the teachings of the '833 patent and the '598 patent application to produce examples of amorphous materials comprising or containing cefuroxime axetil based on case A and case B described above and to determine their glass transition temperatures. Due to the fact that the '833 patent and '598 and '676 patent applications contain examples that employ industrial scale Niro spray-drying systems while my laboratory is equipped with a research scale Buchi spray-drying system, I asked these researchers to utilize the teachings of U.S. patent No. 6,107,290 (the '290 patent) which I was provided with with respect to my first Declaration concerning this matter (the '290 patent, assigned to Woo et al., describes the production of similar amorphous materials as those described in the '833 patent and '598 and '676 patent applications utilizing a Buchi spray-drying system). The results of their efforts are described in the report included as Exhibit B to this my second Declaration with respect to this matter.

11. As described in Exhibit B, the following amorphous phase materials were produced utilizing identical solvents and spray-drying conditions

(i) 100 wt% cefuroxime axetil (case A, GSK)

(i) 91:9 wt%:wt% cefuroxime axetil:sorbitol (case B, Apotex 1)

(iii) 90:9:1 wt%:wt%:wt% cefuroxime axetil:sorbitol:zinc chloride (case B, Apotex 2)

As displayed in Exhibit B, scanning electron microscopy (SEM) images indicate that all samples produced consisted of powders comprised of smooth, spherical particles. For the Apotex 1 and 2 samples, no visual evidence was seen in the SEM images of a phase separation of sorbitol or zinc chloride from cefuroxime axetil (i.e., no crystallites or other nonuniformities were evident in any of the individual smooth, spherical particles comprising the Apotex 1 and 2 samples).

12. With respect to the thermal analysis of the GSK, Apotex 1 and Apotex 2 samples, thermogravimetric analysis results contained in Exhibit B indicate that the samples do not decompose below the melting or glass transition temperature of pure cefuroxime axetil, which confirms that the glass transition temperatures of the samples can be obtained in a straightforward manner via differential scanning calorimetry (DSC). As further described in Exhibit B and summarized in Table 2 from Exhibit B, utilizing a common DSC method for the determination of glass transition temperatures (this method is described in detail in Exhibit B), the following results were obtained:

Sample	**T_g, Run 1**	**T_g, Run 2**	**T_g, Run 3**	**T_g Average**	**Std. Dev.**	**Delta T_g (= $T_{g,\ GSK} - T_{g,\ Apotex}$)**
GSK	78.7	76.9	80.6	**78.7**	1.85	-
Apotex 1	67.6	68.6	65.7	**67.3**	1.47	**11.4**
Apotex 2	70.3	74.3	71.5	**72.0**	2.05	**6.7**

Table 2. Individual run and average T_g's and standard deviations for the spray-dried powders. Delta T_g is defined as the difference between the T_g of the GSK sample and the T_g's of the Apotex samples.

13. As is clearly evident in the table above and described in Exhibit B, a single glass transition temperature was detected for each of the amorphous samples made based on the teachings of the '598 patent application (Apotex 1 and 2), with each transition temperature being significantly lower than the glass transition temperature detected for the amorphous sample made based on the teachings of the '833 patent (GSK). In my opinion, this clearly indicates that the Apotex 1 and 2 samples consist of a molecular level dispersion of cefuroxime axetil and excipient(s) (sorbitol for Apotex 1 and sorbitol and zinc chloride for Apotex 2), with the excipient(s) acting in effect as plasticizers (as I described above, sorbitol is known in some cases to act as a plasticizer in amorphous phases, with plasticizers being defined as materials that lower the glass transition of a given amorphous material). Thus, in my opinion, amorphous materials such as Apotex 1 and 2 described above are clearly not highly pure, substantially amorphous forms of cefuroxime axetil.

14. Thus, in my opinion, these results confirm the fact that amorphous coprecipitates of cefuroxime axetil and excipients such as sorbitol and zinc chloride produced via spray-drying as described in the '598 and '676 patent applications are distinct and different from the highly pure, substantially amorphous forms of cefuroxime axetil produced via spray-drying as described in the '833 patent.

Robert Samuel Langer
Professor of Chemical and Biomedical Engineering
Massachusetts Institute of Technology

AFFIRMED before me)
at Cambridge / M I T)
in Cambridge MA, U.S.A.)
this 5th day of November, 2002)

Constance J. Beal
A Commissioner, Notary Public
for taking Oaths

CONSTANCE J. BEAL
Notary Public
Commonwealth of Massachusetts
My Commission Expires
November 4, 2005

This is Exhibit A referred to in the Declaration of ROBERT SAMUEL LANGER sworn the 5th day of November, 2002.

A Notary Public

CONSTANCE J. BEAL
Notary Public
Commonwealth of Massachusetts
My Commission Expires
November 4, 2005

ROBERT SAMUEL LANGER

Curriculum Vitae

DATE & PLACE OF BIRTH August 29, 1948, Albany, New York

EDUCATION

1974 Sc.D., Chemical Engineering, MIT

1970 B.S. (with distinction) Chemical Engineering, Cornell University

HONORS

2002 Charles Stark Draper Award (National Academy of Engineering)
2002 Othmer Gold Medal (Chemical Heritage Foundation)
2002 Nagai Innovation Award (Controlled Release Society)
2002 Feigenbaum - Levine Lecturer (Beth Israel Hospital at Harvard Medical School)
2002 Honorary Doctorate (Hebrew University of Jerusalem)
2002 Herman Schwan Award (University of Pennsylvania)
2002 Distinguished Lecturer (University of Louisville)
2002 Institute Lecturer (American Institute of Chemical Engineers)
2001 Harrison Howe Award (American Chemical Society)
2001 Seymour J. Kreshover Lecturer (National Institutes of Health)
2001 Ullyot Lecturer (Chemical Heritage Foundation)
2001 Clapp Lecturer (Brown University)
2001 Julian Smith Lecturer (Cornell University)
2001 Mason Lecturer (Stanford University)
2001 Distinguished Lecturer (Carnegie Mellon)
2000 Herman Beerman Lecturer (Society for Investigative Dermatology)
2000 Millennial Lecturer (University of Liverpool)
2000 Bayer Lecture (University of Pittsburgh)
2000 Bayer Stein Honorary Lecture (University of Massachusetts at Amherst)
2000 Honorary Doctorate (The Catholic University of Louvain, Belgium)
2000 Glaxo Wellcome International Achievement Award (Royal Pharmaceutical Society of Great Britain)
2000 Millennial Pharmaceutical Scientist Award (Millennial World Congress of Pharmaceutical Sciences)
2000 William G. Lowrie Lectureship (The Ohio State University)
2000 Frank T. Gucker Lecturer (Indiana University)
2000 First Pierre Galletti Award (American Institute of Medicine & Biological Engineering)
2000 First Patten Distinguished Lectureship (University of Colorado at Boulder)
2000 Wallace Carothers Award (American Chemical Society, Delaware Section)
1999 American Chemical Society Award in Polymer Chemistry
1999 Esselen Award (American Chemical Society, Northeast Section)
1999 G.N. Lewis Medal and Lecturer (University of California at Berkeley)
1999 Beckman Lecturer (University of Illinois at Urbana)
1999 Reilly Lecturership (Notre Dame University)
1999 Ebert Prize (American Pharmaceutical Association)
1998 Outstanding Pharmaceutical Paper Award (Controlled Release Society)
1998 Lemelson-MIT Prize for Invention and Innovation
1998 The Nagai Foundation Tokyo International Prize
1998 Wagner Lectureship (University of Michigan)
1998 Ewing Halsell Foundation Lectureship (University of Texas Health Center, San Antonio)
1998 Robert R. Linton Distinguished Lecture; New England Society for Vascular Surgery
1998 Marcus Memorial Lecturer (Washington University, St. Louis)
1998 Joseph Stokes, Jr. Lecturnship (University of Pennsylvania)
1997 Killian Faculty Achievement Award (MIT)
1997 Wiley Medal (U.S. Food and Drug Administration)
1997 Honorary Doctorate (The Technion - Israel)
1997 William J. Rashkind Memorial Lecture (American Heart Association)
1997 Rohm and Haas Lecturer in Materials Chemistry (University of North Carolina)
1996 Gairdner Foundation International Award

1996 Honorary Doctorate (Eidgenossische Technische Hochschule-ETH, Switzerland)
1996 William Walker Award (American Institute of Chemical Engineers)
1996 Society of Plastics Engineers International Award
1996 Ebert Prize (American Pharmaceutical Association)
1996 Elected a Fellow of Biomaterials Science and Engineering
1996 The Berkeley Lecturer (University of California, Berkeley)
1996 Avis Distinguished Visiting Professor (University of Tennessee)
1995 International John W. Hyatt Service to Mankind Award (Society of Plastics Engineers)
1995 Ebert Prize (American Pharmaceutical Association)
1995 Distinguished Medical Scientist Lecturer (Ohio State University)
1995 Lacy Lecturer (California Institute of Technology
1995 Ralph Peck Memorial Lecturer (Illinois Institute of Technology)
1995 Elected a Fellow (American Association of Pharmaceutical Scientists)
1995 PEL Associates Award (PEL Associates, Groton, Connecticut)
1994 Whitaker Distinguished Lecturer (Biomedical Engineering Society)
1994 Elected to the American Academy of Arts and Sciences
1994 Elected a Fellow, Society of Biomaterials
1994 Miles Lecturer (Cornell University)
1994 Feigenbaum Memorial Lecturer (Beth Israel Hospital, Harvard Medical School)
1993 Distinguished Pharmac. Scient. Award (Highest Honor of the Amer. Assoc.of Pharm.Scient.)
1993 Kurt Wohl Memorial Lecturer (University of Delaware)
1993 Priestley Lecturer (Penn State University)
1992 Elected to the National Academy of Sciences
1992 Elected to the National Academy of Engineering
1992 American Chemical Society Award for Applied Polymer Science (Phillips Award)
1992 Perlman Memorial Award Lecturer (American Chemical Society, Biochemical Technology Division)
1992 Elected a Founding Fellow, American Institute of Medical and Biological Engineering
1992 Kelly Distinguished Lecturer (Purdue University)
1992 Miles Distinguished Lecturer (University of Pittsburgh)
1992 Outstanding Pharmaceutical Paper Award (Controlled Release Society)
1991 Organon Teknika Award (European Society for Artificial Organs)
1991 Charles M.A. Stine Award in Materials Science and Eng. (Am. Institute of Chem.Eng.)
1991 Louis W. Busse Lecturer (University of Wisconsin)
1991 Sidney Riegelman Lecturer (University of California, San Francisco)
1991 Ashton-Cary Lecturer (Georgia Institute of Technology)
1991 Sandoz-Dorsey Lecturer (Ohio State University)
1990 Professional Progress Award (American Institute of Chemical Engineers)
1990 Clemson Award for Basic Research (Society for Biomaterials)
1990 Outstanding Pharmaceutical Paper Award (Controlled Release Society)
1989 Elected to the Institute of Medicine of the National Academy of Sciences
1989 Creative Polymer Chemistry Award (American Chemical Society, Polymer Division)
1989 Outstanding patent in Massachusetts and one of the twenty outstanding patents in the U.S. (Intellectual Property Owners, Inc.)
1989 Founders Award for Outstanding Research (Controlled Release Society)
1989 Walter F. Enz Lecturer (University of Kansas)
1988 Elected to the Gordon Conference Research Council
1988 Elected Chairman, Gordon Conference on Drug Carriers in Biology and Medicine
1988 Robert Rushmer Lecturer (University of Washington, Seattle)
1988 1st Presidential Lecturer, Controlled Release Society (Basel, Switzerland)
1987 Biomedical Research Council Lecturer (University of Michigan)
1986 Food, Pharmaceutical and Bioengineering Award (American Institute of Chemical Engineers)
1986 Elmer L. Linseth Lecturer (Case Western Reserve University)
1983 Outstanding Paper, Institute of Electrical and Electronic Engineering
1983 Merck, Sharpe and Dohme Lecturer (University of Puerto Rico)

1982 Paper Listed as One of the Outstanding Papers of the Year, CHEMTECH
1982 Recipient of the first Dorothy W. Poitras Chair, MIT
1982 Outstanding Teacher Award, MIT Graduate Student Council

EMPLOYMENT

7/88- Kenneth J. Germeshausen Professor of Chemical and Biomedical Engineering, MIT Department of Chemical Engineering; Whitaker College of Health Sciences, Technology, and Management; and the Harvard-MIT Division of Health Sciences and Technology

7/99-6/00 Senior Lecturer on Surgery, Harvard University, Harvard Medical School

7/85-6/88 Professor of Biochemical Engineering, MIT, Department of Applied Biological Sciences, Whitaker College of Health Sciences, Technology, and Management, and the Harvard-MIT Division of Health Sciences and Technology

7/81-6/85 Associate Professor of Biochemical Engineering, MIT, Department of Nutrition and Food Sciences and the Whitaker College of Health Sciences Technology, and Management, and the Harvard-MIT Division of Health Sciences and Technology

7/78-6/81 Assistant Professor of Nutritional Biochemistry, MIT, Deptartment of Nutrition and Food Sciences

7/77-6/78 Assistant Professor of Nutritional Biochemistry, MIT (Visiting), Department of Nutrition & Food Sciences

7/74-present Research Associate, Children's Hospital Medical Ctre., Harvard Med. School, Boston, MA

9/72-6/74 Research Assistant, MIT

9/72-8/73 Chairman, Math and Science Departments, The Group School, Cambridge, MA

PROFESSIONAL AND ACADEMIC ORGANIZATIONS

Controlled Release Society (Elected President, 1991-1992) (Elected to Board of Governors, 1981-1985; Chairman, Regulatory Affairs Committee, 1985-1989).
Biomedical Engineering Society (Elected to the Board of Directors, 1991-1994)
American Institute of Chemical Engineers (Food, Pharmaceutical and Bioeng. Division)
American Chemical Society (Polymer Division)
American Society of Artificial Internal Organs (Program Committee 1984-1987; Membership Committee (1991-93)
International Society of Artificial Internal Organs
Scientific Advisory Board, Department of Chemical Engineering, Georgia Insititute of Technology (1992-2000)
Society for Biomaterials (Elected a Fellow, 1994)
American Association of Pharmaceutical Scientists (Elected a Fellow, 1995)
American Institute of Medical and Biological Engineers (Elected Founding Fellow, 1992; Elected Chair, College of Fellows, 1995)
The Science Board, the United States Food and Drug Administration (FDA) (highest Advisory Board of the FDA), 1995 (Chair since 1999)
Scientific Advisory Board, Schepens Eye Institute, Harvard Medical School (1995-1998)
Board of Scientific Counselors, National Institutes of Health Center for Research Resources (1996-2001)
Scientific Advisory Board, Division of Chemistry and Chemical Engineering, California Institute of Technology (1999-)
Scientific Advisory Board, Department of Chemical Engineering, Princeton University (1999-)
Board of Overseers, Othmer Research Institute, Brooklyn Polytechnic Institute (2001-)
Board of Directors, McGovern Insitute, Massachusetts Institute of Technology (2001-)

COURSES TAUGHT

20.002U	(1977-1988)	Laboratory in Applied Biology
20.S35	(1979-1988)	Pharmacological Engineering
20.11G	(1979-1988)	Analytical Practices in Biochemistry
HST 110	(1979-1981)	Renal Pathophysiology
20.113	(1987-1988)	Problems in Biotechnology
10.02J	(1989-)	Biotechnology and Engineering
10.361	(1989-)	Integrated Chemical Engineering
10.13	(1989-1991)	Thermodynamics
10.984	(1990-)	Biomedical Applications of Chemical Engineering
10.26	(1992-)	Senior Chemical Engineering Project Laboratory

MIT ACTIVITIES

1972-73, 80-	Board of Trustees, MIT Community Service Fund
1972-74	Committee on Preprofessional Advising and Education, MIT
1972-74	Steering Committee, Urban Action, MIT
1977-85	Freshman Advisor
1978-	Undergraduate Advisor
1980-	Premedical Advisory Council, MIT
1977-80	Seminar Committee, Department of Applied Biological Sciences, MIT
1978-80	Asinari Committee, MIT
1979-88	Undergraduate Affairs Committee, Department of Applied Biological Sciences, MIT (Chairman, 1981-1985)
1980-84	MIT-Wellesley Upward Bound Joint Steering Committee
1981-82, 84-85	Financial Aid Committee, Department of Applied Biological Sciences, MIT
1981-86	Admissions Committee, Harvard-MIT Division of Health Sciences and Technology
1983-87	Curriculum Committee, Dept. of Applied Biological Sciences (Chairman, 1985-1987)
1983-87	Radiation Committee, MIT
1983-	Sea Grant Committee, MIT (Chairman, 1993-)
1985-87	Admissions Committee, Harvard MD-POD Program
1986-92	Admissions Committee, MIT Medical Engineering-Medical Physics Program
1986-	Harvard-MIT Joint Committee on Health Sciences and Technology
1988	Search Committee for Department Head, Department of Chemical Engineering
1988-1992	Admissions Committee, Department of Chemical Engineering
1989-1991	Undergraduate Committee, Department of Chemical Engineering
1991-1993	Seminar Chairman, Department of Chemical Engineering
1993-	Board of Advisors, MIT Industrial Summer Session Program
1994- 1995	Selection Committee for Co-Director of Harvard-MIT HST Program
2000-	Harvard-MIT Division of Health Sciences and Technology Advisory Council

EDITORIAL BOARDS

1983-	BIOMATERIALS- Editor
1987-	BIOMATERIALS, ARTIFICIAL CELLS, AND IMMOBILIZATION TECHNOLOGY (Associate Editor, 1991-)
1983-92	SELECTIVE CANCER THERAPEUTICS (CANCER DRUG DELIVERY)
1983	METHODS OF ENZYMOLOGY-DRUG DELIVERY SYSTEMS
1984-98	JOURNAL OF CONTROLLED RELEASE
1985-	BIOMEDICAL POLYMERS
1986-	ADVANCED DRUG DELIVERY SYSTEMS
1987-	DRUG DESIGN AND DELIVERY
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1994-	JOURNAL OF PHARMACEUTICAL SCIENCE
1995-	TISSUE ENGINEERING
1995-	THE ENCYCLOPEDIA OF CONTROLLED DRUG DELIVERY
1996-	BIRKHAUSER: SYNTHETIC BIODEGRADABLE POLYMER SCAFFOLDS
1996-98	NANOBIOLOGY
1997-99	CHEMICAL AND ENGINEERING NEWS
1997-99	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES

1997- ANNUAL REVIEWS OF BIOMEDICAL ENGINEERING
1997- BIOMEDICAL MICRODEVICES
1998- DIABETES TECHNOLOGY & THERAPEUTICS
1999- JOURNAL OF POLYMER SCIENCE, CHEMISTRY
1999- PHARMACEUTICAL SCIENCE
1999- REGENERATIVE MEDICINE
1999- METHODS OF TISSUE ENGINEERING
1999- ANGEWANDTE CHEMIE
2000- EUROPEAN JOURNAL OF PHARMACEUTICAL SCIENCES
2002- JOURNAL OF INVESTIGATIVE DERMATOLOGY-Associate Editor

PATENTS

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1. US Patent 4,164,560: Folkman, J., Langer, R., Systems for the Controlled Release of Macromolecules.
2. US Patent 4,341,869: Langer, R., Linhardt, R., Cooney, C., Galliher, P., Process of Producing of Heparinase.
3. US Patent 4,357,312: Hsich, D., Langer, R., Method of Making Prolonged Release Body.
4. US Patent 4,373,023: Langer, R., Linhardt, R., Cooney, C., Galliher, P., Flanagan, M., Klein, M., Process for Neutralizing Heparin.
5. US Patent 4,391,797: Folkman, J., Langer, R., Systems for the Controlled Release of Macromolecules.
6. US Patent 4,396,762: Langer, R., Linhardt, R., Cooney, C., Fitzgerald, Grant, A., Heparinase Derived Anticoagulants.
7. US Patent 4,414,147: Klibanov, A., Langer, R., Methods of Decreasing the Hydrophobicity of Fibroblast and other Interferons.
8. US Patent 4,443,545: Langer, R., Lindhardt, R., Cooney, C., Galliher, P., A Process for Producing Heparinase.
9. US Patent 4,501,116: Folkman, M., Taylor, S., Langer, R., Inhibition of Angiogenesis.
10. US Patent 4,591,496: Cohen, J., Siegel, R., Langer, R., Process for Making Systems for The Controlled Release of Macromolecules.
11. US Patent 4,638,045: Kohn, J., Langer, R., Non-Peptide Polyamino Acid Bioerodible Polymers.
12. US Patent 4,657,543: Kost, J., Langer, R., Ultrasonically Modulated Polymeric Devices for Delivery Composition.
13. US Patent 4,666,855: Yang, V., Langer, R., Rapid Method for Determining the Isoelectric Point for Amphoteric Molecules.
14. US Patent 4,732,155: Zetter, B., Langer, R., Implantable Chemoattractant System.
15. US Patent 4,753,652: Levy, R., Langer, R., Biomaterial Implants whuch Resist Calcification.
16. US Patent 4,757,128: Domb, A., Langer, R., High Molecular Weight and Preparation of Polyanhydride Thereof.
17. US Patent 4,767,402: Kost, J., Levy, D., Langer, R., Ultrasound Enhancement of Transdermal Drug Delivery.
18. US Patent 4,779,806: Langer, R., Kost, J., Ultrasonically Modulated Polymeric Devices For Delivering Compositions.
19. US Patent 4,780,212: Kost, J., Langer, R., Ultrasound Enhancement of Membrane Permeability.
20. US Patent 4,789,724: Domb, A., Langer, R., Preparation of Anhydride Copolymers.
21. US Patent 4,795,703: Hannon, R., Thompson, R., Langer, R., Folkman, J., Heparinase Assay.
22. US Patent 4,806,621: Kohn, J., Langer, R., Biocompatible, Bioerodible, Hydrophobic, Implantable Polyimino carbonate article.
23. US Patent 4,846,786: Freed, L. B., Kadam, J., Drinker, P.A., Thebeau, J., Langer, R., Bioreactor Containing Suspended, Immobilized Species.
24. US Patent 4,857,311: Domb, A., Langer, R., Polyanhydrides with Improved Hydrolytic Degradation Properties.
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This is Exhibit B referred to in the Declaration of ROBERT SAMUEL LANGER sworn the 5th day of November, 2002.

A Notary Public

CONSTANCE J. BEAL
Notary Public
Commonwealth of Massachusetts
My Commission Expires
November 4, 2005

Report of Experimental Results
Langer Laboratory
Massachusetts Institute of Technology
October 30, 2002

Production and Thermal Analysis of Amorphous Powders Containing (i) Cefuroxime Axetil, (ii) Cefuroxime Axetil and Sorbitol and (iii) Cefuroxime Axetil, Sorbitol and Zinc Chloride

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Summary:

Amorphous powders containing (i) pure cefuroxime axetil (identified as GSK), (ii) a combination of cefuroxime axetil and sorbitol (identified as Apotex 1) and (iii) a combination of cefuroxime axetil, sorbitol and zinc chloride (identified as Apotex 2) were produced via spray-drying based on formulations and methods described in U.S. Patent Application No. 09/485,598 and copending application No. 09/621,676 (the '598 and '676 patent applications, respectively, these applications being utilized to define the Apotex 1 and 2 compositions described below as well as for the selection of spray-drying solvents) and U.S. Patents No. 4,820,833 (the '833 patent, this patent being utilized to define the GSK composition described below as well as for the selection of spray-drying solvents) and 6,107,290 (the '290 patent, this patent being used as a guide for the selection of spray-drying conditions for the utilization of a Buchi spray-dryer as well as for the selection of spray-drying solvents). The powders and raw materials were imaged via scanning electron microscopy to determine their morphology. The powders were then subjected to two methods of thermal analysis, thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) to determine their thermal transition properties. The results of this analysis showed that Apotex 1 and 2 spray-dried powders referred to above have decreased glass transition temperatures relative to the pure amorphous cefuroxime axetil spray-dried powder identified as GSK sample above, indicating that the Apotex 1 and 2 powders do not constitute nor contain appreciable amounts of pure amorphous cefuroxime axetil.

Formulation and Powder Production:

1. Compositions

The following compositions were spray-dried as described further below:

(i) 100 wt% cefuroxime axetil (GSK)
(i) 91:9 wt%:wt% cefuroxime axetil:sorbitol (Apotex 1)
(iii) 90:9:1 wt%:wt%:wt% cefuroxime axetil:sorbitol:zinc chloride (Apotex 2)

2. Solution Preparation

For the purposes of identifying a common solvent system for the spray-drying of the three compositions listed above, the solubility of the various compounds in the solvent systems identified in the patents and patent application listed above was assessed, singly and in combination. A suitable solvent system was found to be at about 10% (v/v) water to 90% (v/v) of (90% (v/v) acetone:10% (v/v) methanol).

For spray-drying, the solutes were dissolved separately in the chosen solvent system (see below), and the resulting solutions were mixed as follows (note that in order to maintain uniformity in the processing of samples, all samples were mixed with 10% v/v water, even if this was not mandated by drug solubility).

(i) GSK:
500 mg cefuroxime were dissolved in 4.5 ml of 90% (v/v) acetone, 10% (v/v) MeOH. Subsequently, 0.5 ml water was added dropwise w/ frequent vortexing.

(ii) Apotex 1:
500 mg cefuroxime was dissolved in 4.5 ml of 90% (v/v) acetone, 10% (v/v) MeOH. Next, 0.5 ml of water containing 50 mg sorbitol was added dropwise with vortexing.

(iii) Apotex 2:
500 mg cefuroxime was dissolved in 4.5 ml of 90% (v/v) acetone, 10% (v/v) MeOH. Next, 0.5 ml of water containing 50 mg sorbitol and 5 mg zinc chloride was added dropwise with vortexing.

3. Spray drying

Prior to initiating these experiments, a Buchi Model 190 spray dryer was taken apart, cleaned thoroughly and fitted with new tubing to minimize contamination. In all runs, entry of the sample was preceded by 30 min of running acetone:methanol:water::81:9:10 in order to ensure stability of the outlet temperature. Runs were conducted utilizing the spray-drier settings listed below.

Drying gas (air) flowrate setting = 620
Inlet temperature = 49 to 51 °C
Outlet temperature = 37 °C
Aspirator setting = -15
Solvent flowrate = 2.2 ml/min.

Spray-drying was followed by a 10-minute cool-down period after which the system was turned off. All runs resulted in the production of yellowish powders with yields of approximately 25 percent for the GSK powder and approximately 40 percent for both Apotex 1 and 2 powders.

Scanning Electron Microscopy Analysis:

Samples were prepared for SEM analysis by placing a small amount of each powder on an aluminum stub and coating with gold in PelCo SC-6 sputter coater for a total of 150 seconds. The first 50 seconds were at 10 milliamps, in two 25-second intervals separated by a five second pause. The samples were then coated twice for 5 x 10 seconds with a 10-second pause between each 10-second sputtering interval. Samples were observed in a Hitachi S-530 Scanning Electron Microscope (SEM).

SEM photographs of samples of the spray-dried compositions GSK, Apotex 1 and Apotex 2 are shown in Figures 1 through 9 below. Photos were taken at 50, 300, and 3000x magnifications. As shown in Figures 1 through 3 below, the GSK formulation exhibited dense, cohesive aggregates of smooth, nearly spherical particles of approximately one to two microns in diameter. As shown in Figures 4 through 9 below, the Apotex 1 and 2 powders appeared to be aggregates of very smooth, spherical particles of sizes ranging from one to ten microns.

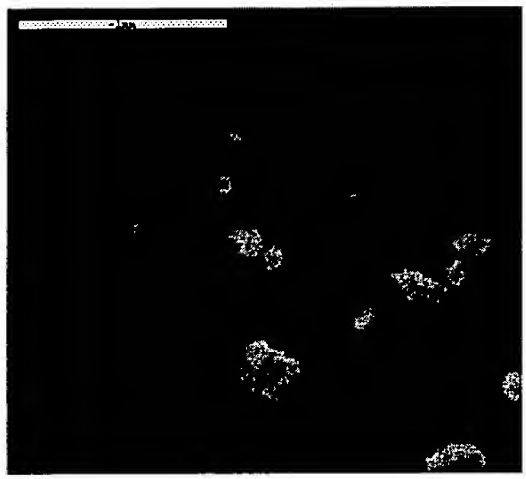

Figure 1. GSK at 50x

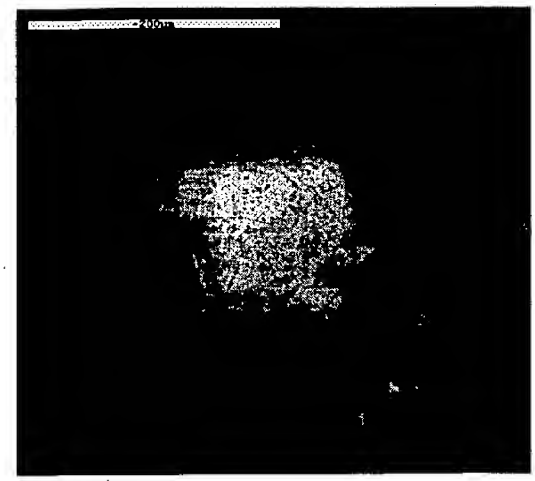

Figure 2. GSK at 300x

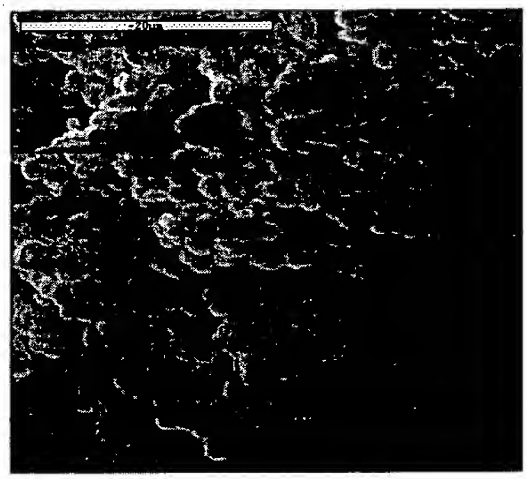

Figure 3. GSK at 3000x

Figure 4. Apotex 1 at 50x

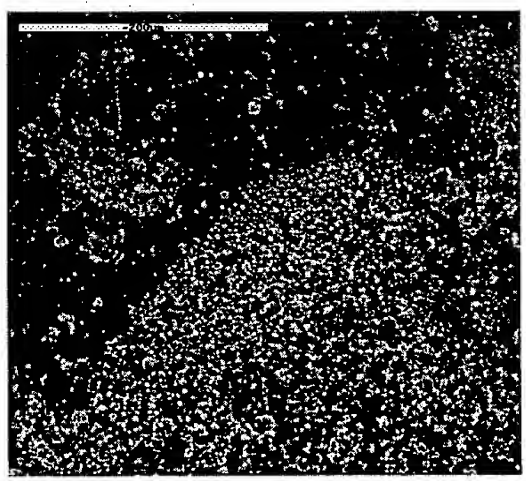

Figure 5. Apotex 1 at 300x

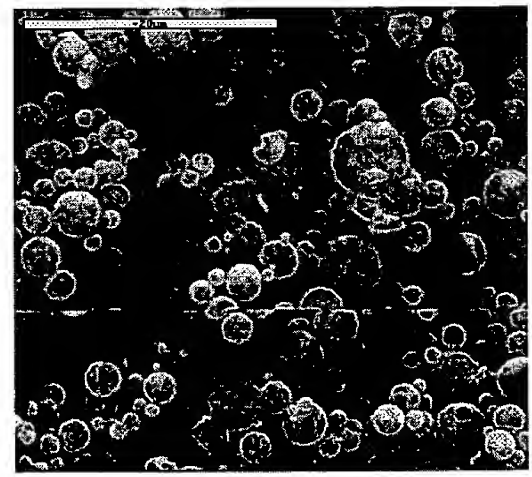

Figure 6. Apotex 1 at 3000x

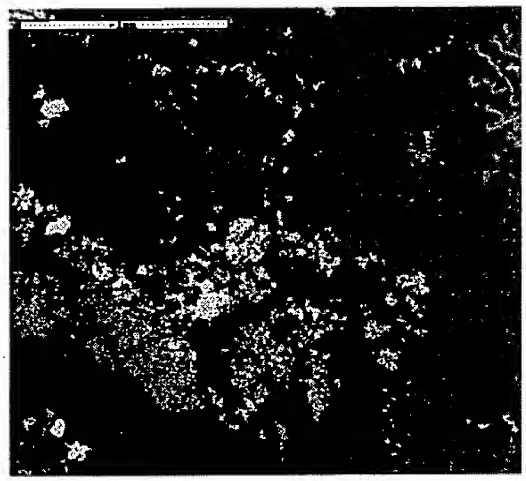

Figure 7. Apotex 2 at 50x

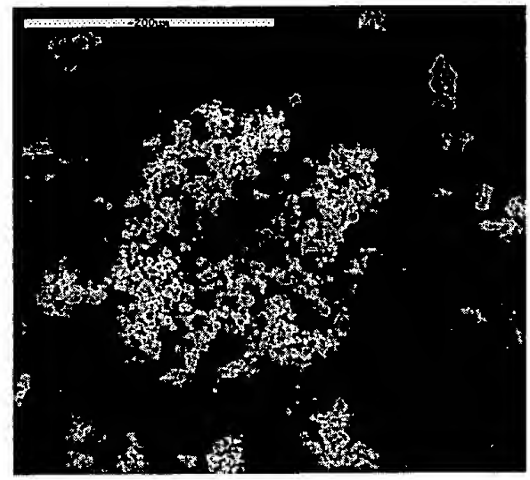

Figure 8. Apotex 2 at 300x

Figure 9. Apotex 2 at 3000x

Thermogravimetric Analysis

Thermogravimetric Analysis (TGA) was performed prior to performing Differential Scanning Calorimetry (DSC) in order to ensure that the materials would not decompose within the temperature range investigated. As stated in the '290 patent (column 1, line 19), crystalline cefuroxime axetil has a melting point of 180 °C. One could estimate based on this melting temperature that the glass transition temperature (T_g) of amorphous cefuroxime axetil should be in the neighborhood of 60 to 80 °C based on known ratios of T_g to melting temperatures of common pharmaceuticals (as described in the reference authored by Fukuoka et al. attached as Appendix A to this report). Thus, an upper temperature limit for the detection of T_g's in the spray-dried samples was chosen to be 120 °C, with TGA being utilized to confirm a lack of decomposition up to this temperature. Samples were analyzed on a PerkinElmer TGA 7 with nitrogen purge. The samples were heated in platinum pans from 30 to 900 °C at a heating rate of 20 °C/minute. Results are shown in the Figures 10 through 14 below.

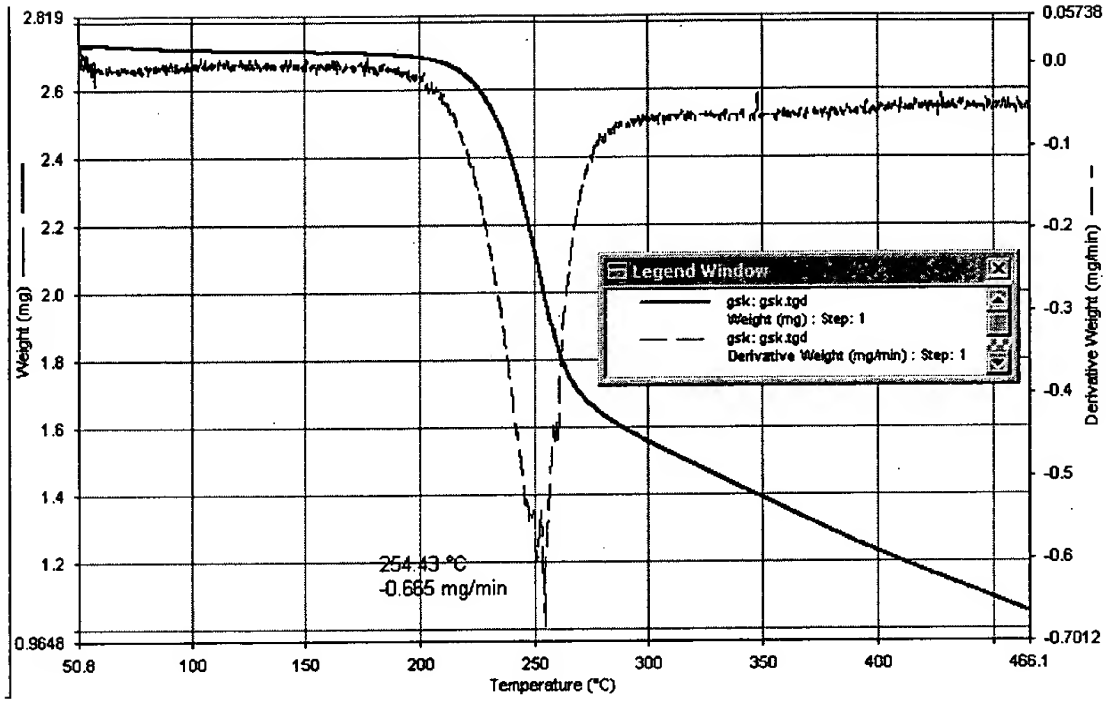

Figure 10. TGA scan obtained for the GSK powder.

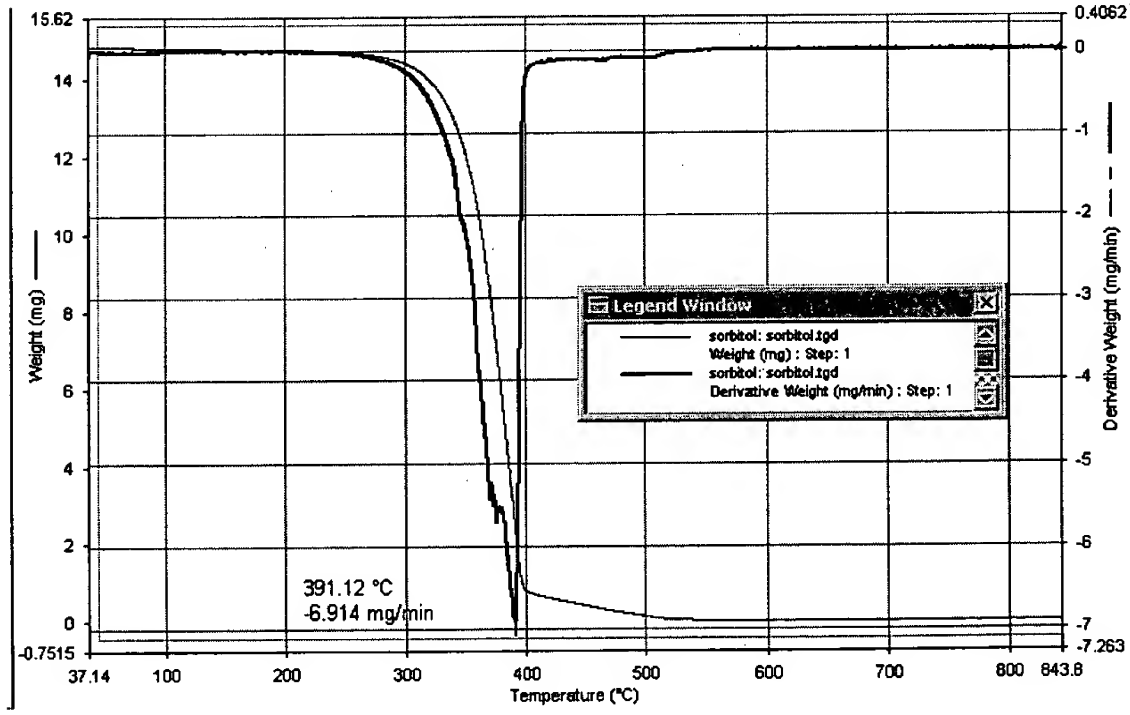

Figure 11. TGA scan obtained for the sorbitol sample.

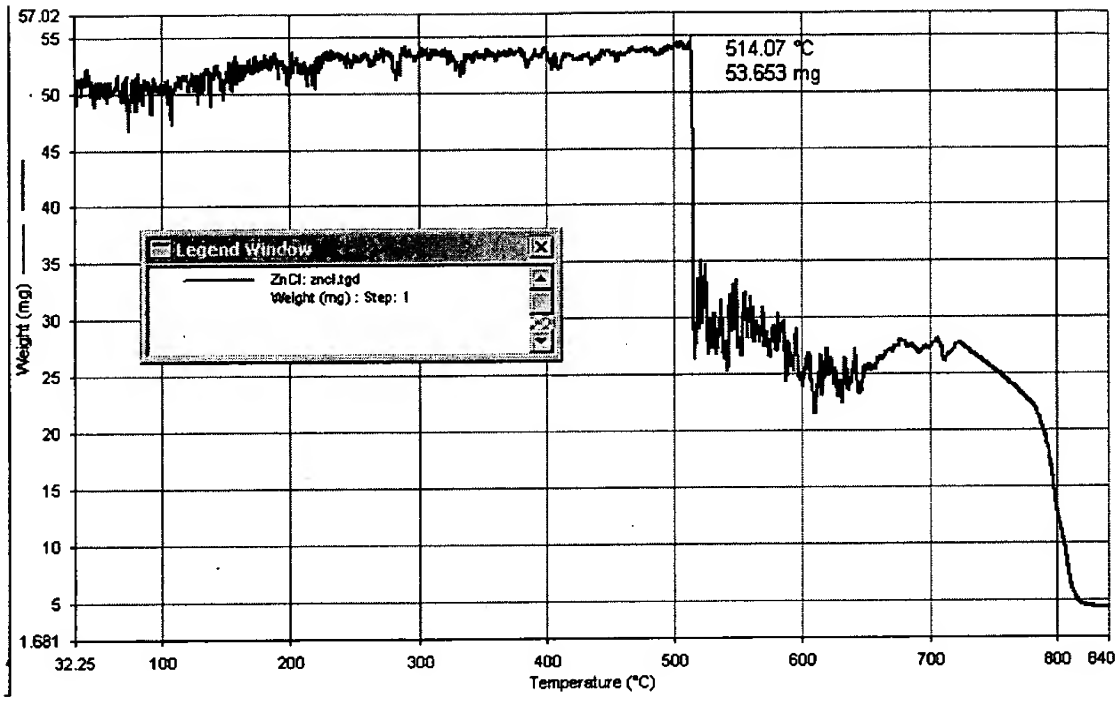

Figure 12. TGA scan obtained for the zinc chloride sample.

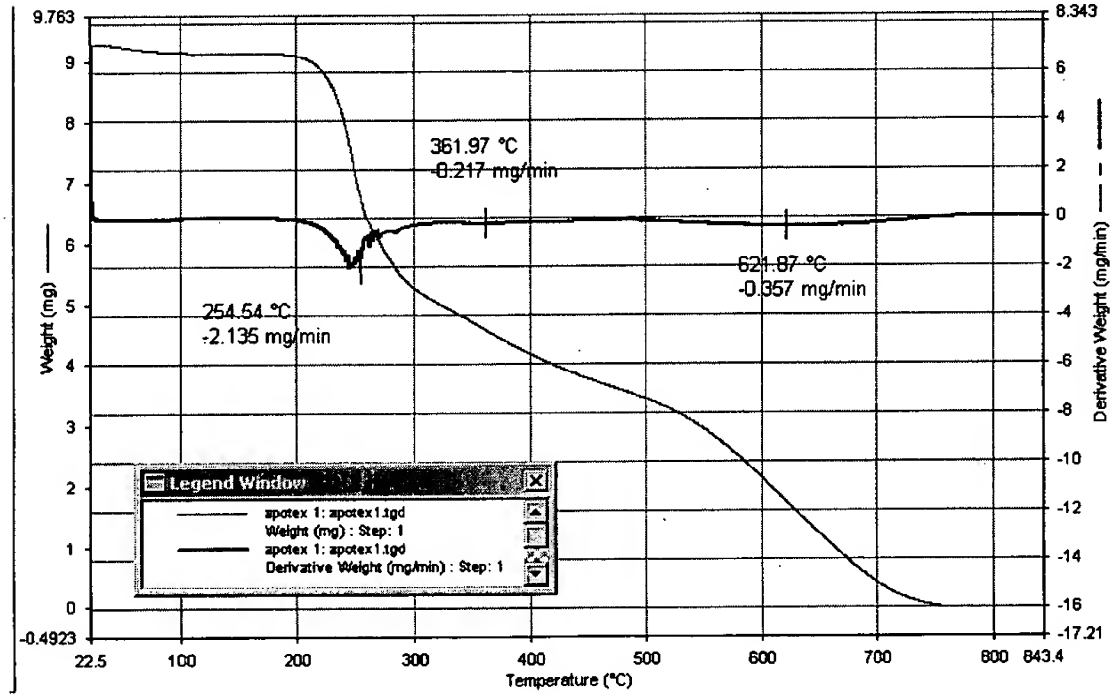

Figure 13. TGA scan obtained for the Apotex 1 powder.

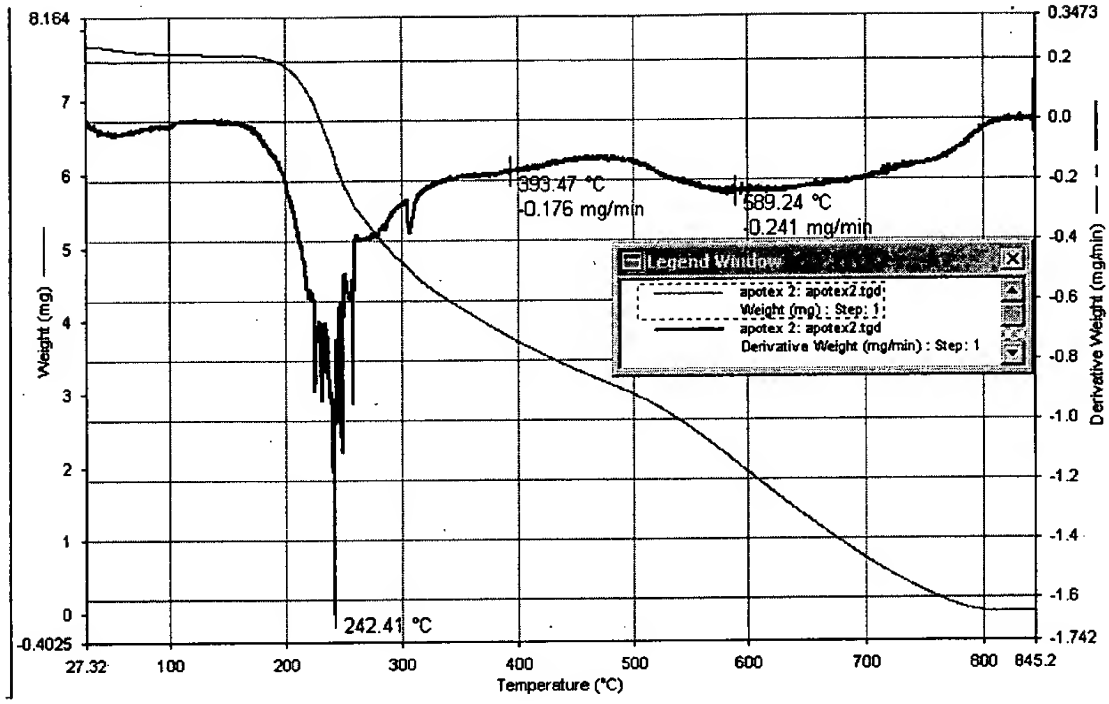

Figure 14. TGA scan obtained for the Apotex 2 powder.

As displayed in Figure 10, the GSK powder containing 100% cefuroxime axetil displayed a decomposition temperature of 254 °C. Before the Apotex powder samples were run, TGA scans were obtained for pure sorbitol and zinc chloride to aid in interpretation of the results. As displayed in Figure 11, the sorbitol sample displayed a decomposition temperature of 391 °C. As displayed in Figure 12, the zinc chloride sample displayed a step weight loss at 514 °C. As displayed in Figure 13, the Apotex 1 powder sample showed a fairly continuous weight loss starting around 200 °C, with slope inflection points at approximately 254 and 361 °C, most likely corresponding to the decomposition of the cefuroxime axetil and sorbitol, respectively based on the results seen for the GSK and sorbitol samples described above. As displayed in Figure 14, the Apotex 2 powder showed inflection points at 242, 393, and 593 °C, most likely corresponding to the decomposition or boiling of cefuroxime axetil, sorbitol and zinc chloride, respectively, based again on the results seen for the GSK, sorbitol and zinc chloride samples described above. Thus, with respect to the determination of the glass transition temperatures of the spray-dried powders, the TGA results described above indicated that all spray-dried samples and raw materials are stable below 200 °C, well above the expected and measured glass transition temperatures of the spray-dried powders as described below.

Differential Scanning Calorimetry Analysis

The amorphous spray-dried samples were analyzed on a Perkin Elmer Diamond DSC system with Intracooler (N_2 purge gas). Samples were analyzed in 30 µL Autosampler aluminum pans (PerkinElmer part #B0143016) with vented lids. Baseline subtraction was used to account for the heat flow to the reference pan. PerkinElmer Pyris Manager software was used to process the data. For the determination of glass transition temperatures, a cyclic heating mode utilizing a temperature ramp of 20 °C /minute over a temperature range of 40 to 120 °C was employed, with the second heating cycle being utilized to determine T_g (this procedure is described in detail in the Perkin Elmer technical guide which is attached as Appendix B to this report). Three runs (n = 3) were conducted for each sample, with JMP statistical analysis software utilized to determine mean T_g values and perform an analysis of variance and error and also to compare the mean T_g values via a Students t test (a description of these tests is attached as Exhibit C to this report). The DSC operating conditions are summarized in Table 1 below.

Sample	Minimum Temp. (°C)	Maximum Temp. (°C)	Heating Rate (°C /min)	Number of Heating Cycles
GSK	40	120	20	2
Apotex 1	40	120	20	2
Apotex 2	40	120	20	2

Table 1. Sample weights and heating rates for samples undergoing DSC analysis.

Figures 15 through 17 show examples of the resultant DSC scans for the GSK, Apotex 1 and Apotex 2 samples (each sample was analyzed three times as described above). T_g was calculated for each sample using the half C_p (heat capacity) method on the second heating cycle. As shown in Figure 15, the first GSK sample analyzed showed a T_g of 78.7 °C on the second heating cycle. Subtraction of the second heating curve from the first yielded a curve that shows the irreversible components (enthalpic relaxation) of the heating curve. For this sample the irreversible curve showed a peak at 80.6 °C with a change in enthalpy (ΔH) of 7.92 J/g. As shown in Figure 16, the first Apotex 1 sample analyzed showed a T_g of 67.6 °C on the second heating cycle. The irreversible curve shows a peak at 76.9 °C with a ΔH of 7.51 J/g. As shown in Figure 17, the first Apotex 2 sample analyzed showed a T_g of 70.3 °C on the second heating cycle. The irreversible peak occurred at 77.8 °C and had a ΔH of 6.72 J/g.

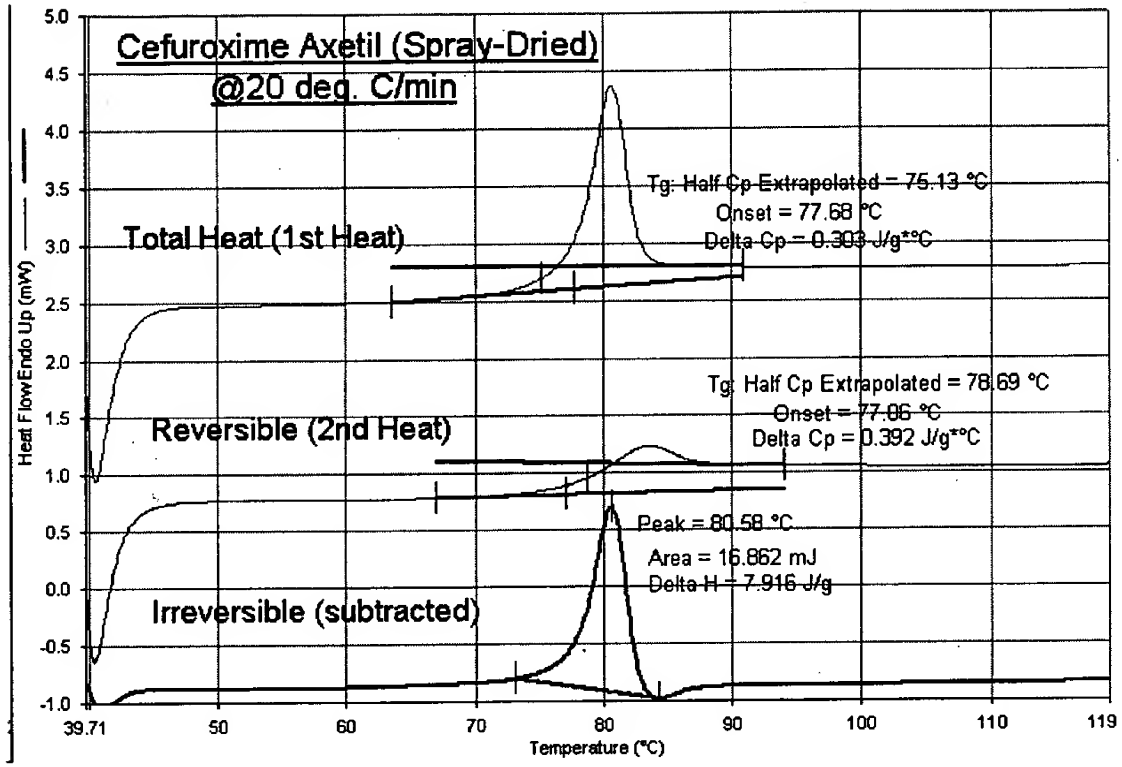

Figure 15. Cyclic DSC scan for the GSK spray-dried sample.

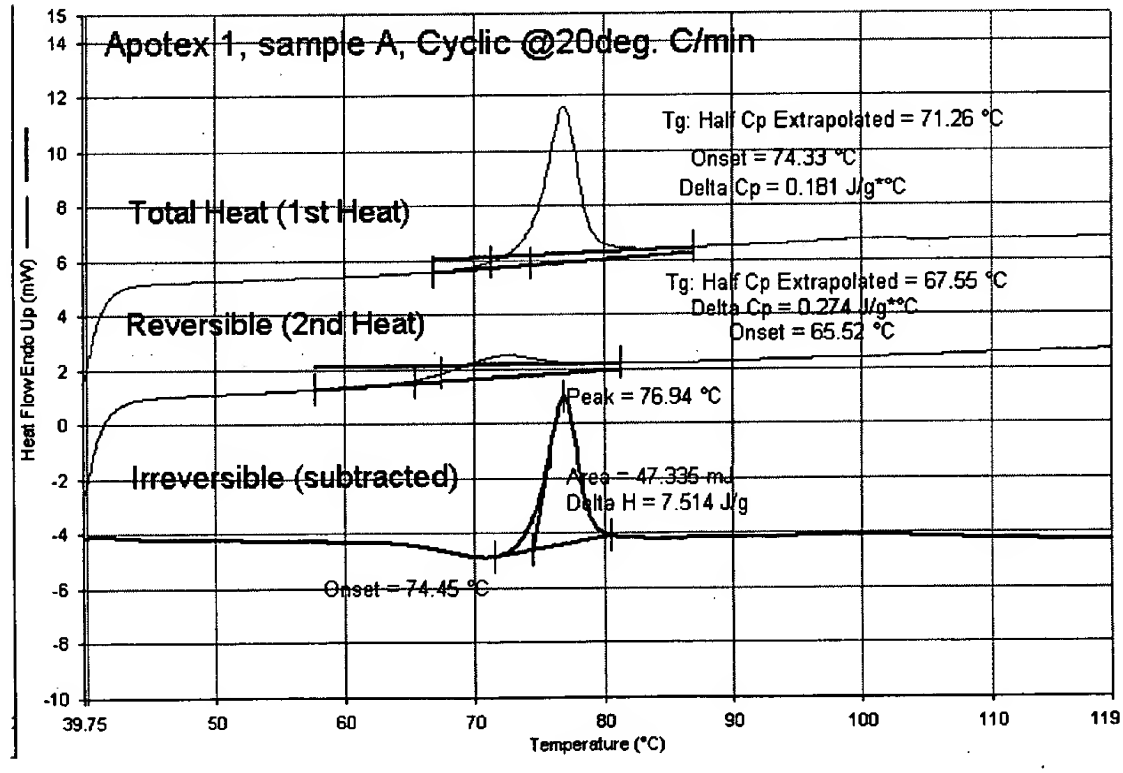

Figure 16. Cyclic DSC scan for the Apotex 1 spray-dried sample.

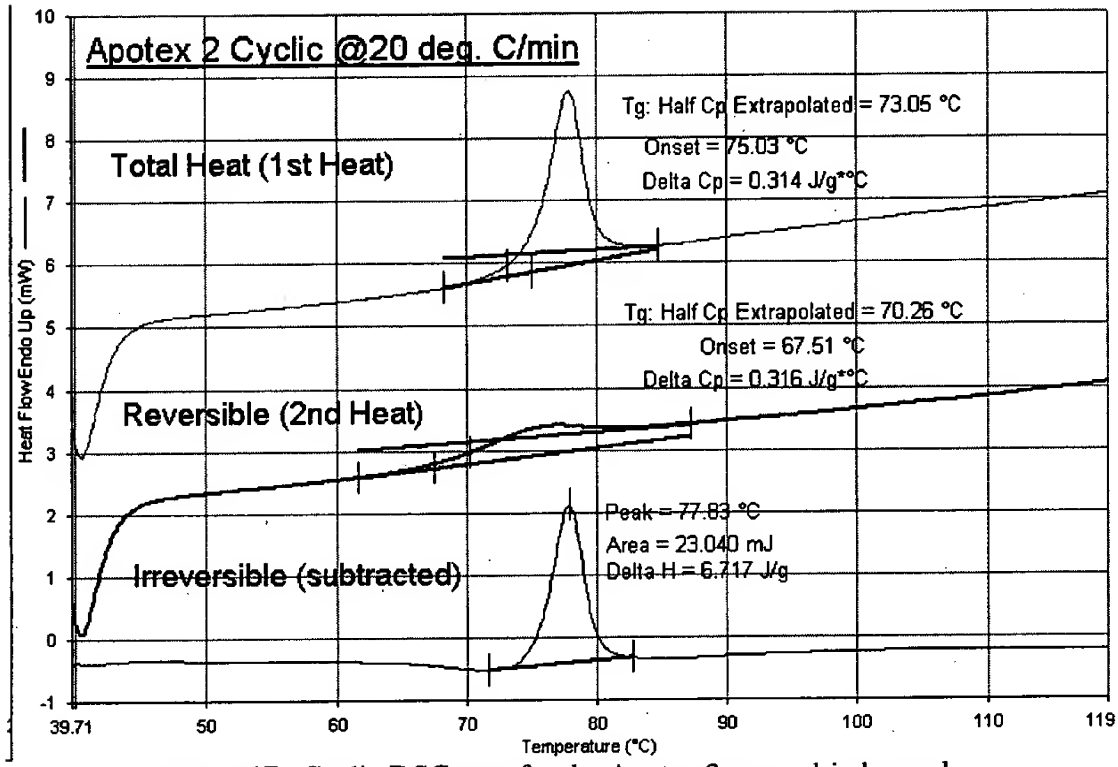

Figure 17. Cyclic DSC scan for the Apotex 2 spray-dried sample.

A summary of the DSC results and their statistical analysis is shown in Tables 2 below. Both Apotex 1 and 2 samples have T_g's that are significantly lower that the T_g of the GSK sample, with the T_g of the Apotex 1 sample being 11.4 °C lower than the T_g of the GSK sample and the T_g of the Apotex 2 sample being 6.7 °C lower than the T_g of the GSK sample. The results of the Students t test confirm that these differences in T_g are statistically significant. Additionally, only one T_g was observed to be present for each of the Apotex samples, which indicates the presence of a uniform dispersion of cefuroxime axetil and sorbitol for Apotex 1 and cefuroxime axetil, sorbitol and zinc chloride for Apotex 2. Thus, these results indicate that the added excipients sorbitol and zinc chloride in the Apotex spray-dried powder samples are intimately mixed on a molecular level with the cefuroxime axetil and act as plasticizers to reduce the T_g of the compositions. No evidence was seen to support the hypothesis that a pure amorphous phase of cefuroxime axetil is present in the Apotex 1 or 2 samples.

Sample	T_g, Run 1	T_g, Run 2	T_g, Run 3	T_g Average	Std. Dev.	P-value	Delta T_g (= $T_{g,\ GSK} - T_{g,\ Apotex}$)
GSK	78.7	76.9	80.6	**78.7**	1.85	**0.001**	-
Apotex 1	67.6	68.6	65.7	**67.3**	1.47	**0.014**	**11.4**
Apotex 2	70.3	74.3	71.5	**72**	2.05	**0.031**	**6.7**

Table 2. Individual run and average T_g's and standard deviations for the spray-dried powders. P-value was calculated using a two-tailed, unpaired student t-test. Delta T_g is defined as the difference between the T_g of the GSK sample and the T_g's of the Apotex samples.

Conclusions

The SEM photos show that the GSK, Apotex 1, and Apotex 2 have very smooth spherical particles, with the Apotex 1 and Apotex 2 particles being larger in size. The TGA results indicated that none of the materials would decompose within the DSC temperature range of interest. The DSC results and statistical analysis indicate that both the Apotex 1 and Apotex 2 spray-dried samples have statistically significant lower T_g's than the GSK spray-dried sample, indicating that the Apotex 1 and 2 samples likely consist of molecular level dispersions of cefuroxime axetil and excipients. Thus, these results indicate that a pure amorphous phase of cefuroxime axetil does not appear to be present in the Apotex 1 and 2 samples.

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Glassy State of Pharmaceuticals. V.[1] Relaxation during Cooling and Heating of Glass by Differential Scanning Calorimetry[2]

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Glassy pharmaceuticals were prepared by cooling the melts and their state was confirmed by measuring the glass transition temperature (T_g) and the anomalous endothermic peak (heat capacity maximum) in the differential scanning calorimetry (DSC) curves. Glass formation was newly discovered for 24 pharmaceuticals including acetaminophen, chloramphenicol, flufenamic acid and proxyphylline. The value of the ratio of T_g and melting temperature (T_m) of these pharmaceuticals lay between 0.69 and 0.85. The rate and quantity of relaxation of glass was determined by the area under the anomalous endothermic peak of the DSC curves of glasses prepared at various cooling rates, that of glassy griseofulvin was found to have the largest among the pharmaceuticals examined. The apparent activation energy of glass transition of chenodeoxycholic acid, griseofulvin and tolnaftate prepared at the cooling rate of −1.25 K/min was calculated to be 273.6, 270.3 and 127.6 kJ/mol, respectively. The influence of heating rate on T_g and the area under the anomalous endothermic peak of the DSC curve of glassy aspirin both immediately and after standing for 60 min at 232 K following preparation of the glass was examined. Both factors decreased as heating rate decreased. The apparent activation energy of glass transition of both samples of aspirin was calculated to be 105.6 kJ/mol.

Keywords glassy state; pharmaceutical; glass transition temperature; apparent activation energy; relaxation process; differential scanning calorimetry; X-ray analysis

In previous papers,[1,3] the existence of the glassy state of indomethacin was confirmed by detection of a jump of heat capacity and the anomalous endothermic peak in differential scanning calorimetry (DSC) curves. The thermal properties, the relaxation process, the rate of dissolution and the rate of crystallization of glassy pharmaceuticals were investigated. Their mechanical properties were also studied by TMA (thermomechanical analysis). For indomethacin it was reported that the bioavailability of glass was better than that of crystal.[3]

In the present paper, 24 glassy pharmaceuticals were newly prepared by cooling the melts and the glassy state was confirmed by detection of a jump of heat capacity and the anomalous endothermic peak in the DSC curves. The relationship between the glass transition temperature (T_g) and melting temperature (T_m) was investigated. It was found earlier[3] that relaxation of glassy indomethacin occurred during cooling, heating and isothermal aging below T_g. Here the influence of cooling and heating rates on relaxation of some glassy pharmaceuticals was investigated and the apparent activation energy of glass transition was calculated.

Experimental

Materials Materials used were all of reagent grade.

Preparation of Glass The glass was prepared in the same way as reported previously.[3]

Thermal Analysis A Perkin Elmer DSC-2 differential scanning calorimeter equipped with an Intracooler I system was used. Measurement conditions were the same as those reported,[3] as was determination of the area under the anomalous endothermic peak.

Thin-Layer Chromatography (TLC) The chemical stability of pharmaceuticals during treatment of the sample was checked using TLC. Measurement conditions of TLC were the same as reported earlier[1] and spots were detected under ultraviolet light.

Results and Discussion

1) Glass Transition Temperature of Glassy Pharmaceuticals Table I shows the T_g, T_m and the T_g/T_m values of the pharmaceuticals newly found. The T_g values of glassy dibucaine and mephenesin were the lowest among these pharmaceuticals, while glassy brucine, griseofulvin and 4 cholic acid had relatively high T_g values. No decomposition during treatment of the sample was observed by TLC.

2) Relationship between T_g and T_m It is known that T_g/T_m is, as a rough rule, about 0.5 for many symmetrical polymers such as polyethylene and 0.7 for many asymmetrical polymers such as polyisoprene.[4] It was reported[1] that the T_g/T_m values of glassy pharmaceuticals lay between 0.59 and 0.84 and were slightly larger than those of polymers. As shown in Table I, the T_g/T_m values of glassy pharmaceuticals lay between 0.69 and 0.85. Figure 1 shows the relationship between T_g and T_m of glassy pharmaceuticals containing the samples previously reported.[1] Pharmaceuticals newly found to form glass are

TABLE I. Pharmaceuticals Newly Found to Form Glass

Pharmaceutical	T_g (K)	T_m (K)	T_g/T_m
Dibucaine	246	336	0.73
Mephenesin	247	340	0.73
Ethacrynic acid	282	398	0.71
Tolbutamide	284	403	0.70
Tolnaftate	287	384	0.75
Flufenamic acid	290	406	0.71
Proxyphylline	295	403	0.73
Eserine	297	378	0.79
Nialamide	297	427	0.70
Chlorotrianisene	298	393	0.76
Acetaminophen	302	441	0.69
Chloramphenicol	306	414	0.74
Estradiol-17β-cypionate	309	425	0.73
Dyphylline	315	438	0.72
Norethynodrel	324	453	0.72
Spironolactone	331	478	0.69
Chlormadinone acetate	334	483	0.69
β-Estradiol-3-benzoate	336	472	0.71
Brucine	365	451	0.81
Griseofulvin	370	497	0.74
Chenodeoxycholic acid	371	436	0.85
Deoxycholic acid	377	447	0.84
Ursodeoxycholic acid	378	477	0.79
Cholic acid	393	473	0.83

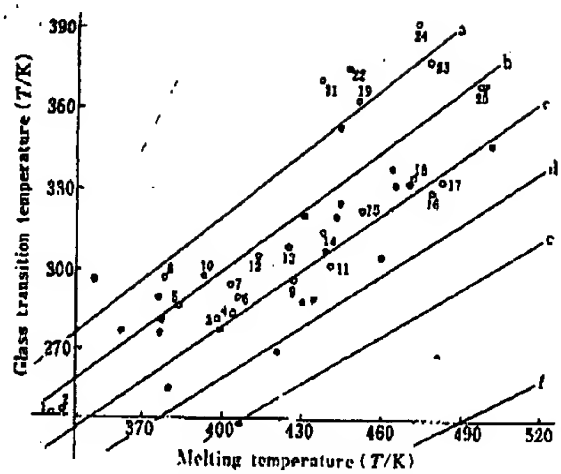

Fig. 1. Relationship between T_g and T_m of Various Pharmaceuticals

The oblique lines originate from the absolute zero point and the slopes give T_g/T_m. The pharmaceuticals newly found to form glass are expressed as open circles and those previously reported to form glass as closed circles. a, 0.80; b, 0.75; c, 0.70; d, 0.65; e, 0.60; f, 0.50. 1, dibucaine; 2, mephenesin; 3, ethacrynic acid; 4, tolbutamide 5, tolnaftate, 6, flufenamic acid; 7, proxyphylline; 8, eserine; 9, nialamide; 10, chlorotrianisene; 11, acetaminophen; 12, chloramphenicol; 13, estradiol-17β-cypionate; 14, dyphylline; 15, norethynodrel; 16, spironolactone; 17, chlormadinone acetate; 18, β-estradiol-3-benzoate; 19, brucine; 20, griseofulvin; 21, chenodeoxycholic acid; 22, deoxycholic acid; 23, ursodeoxycholic acid; 24, cholic acid.

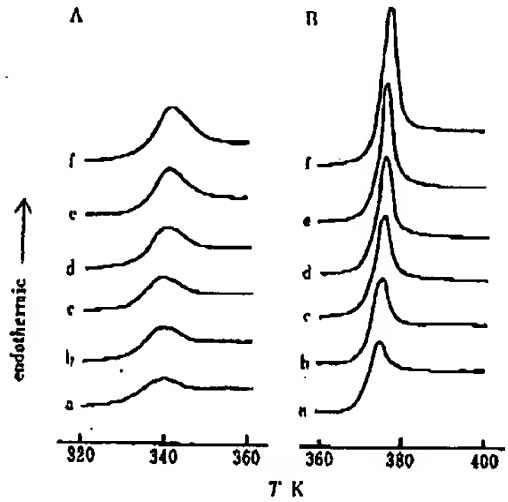

Fig. 2. DSC Curves at Heating Rate of 40 K/min of Glassy Spironolactone and Griseofulvin Prepared at Various Cooling Rates

A, spironolactone; B, griseofulvin. Cooling rate in preparation: a, quenching, b, −10; c, −5; d, −2.5; e, −1.25; f, −0.62 K/min.

expressed as open circles and those previously reported to form glass as closed circles. The oblique lines originate from the absolute zero point and the slopes of the lines give the T_g/T_m. The T_g/T_m values of almost all pharmaceuticals were distributed in the range of 0.65 to 0.80, those of chenodeoxycholic acid, deoxycholic acid and cholic acid having steroid structure were the largest among the samples examined.

3) Relaxation of Glass during Preparation at Various Cooling Rates It has been recognized that T_g of the glass formed increased and the anomalous endothermic peak became larger with decrease in the cooling rate of the melt.[3] Also, for isothermal aging of glassy indomethacin below T_g

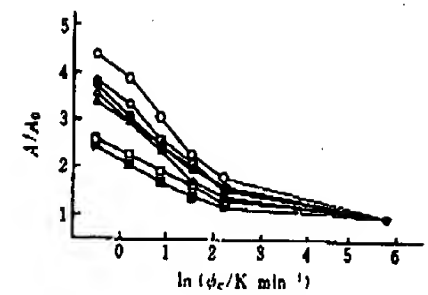

Fig. 3. Effect of Cooling Rate on the Area under the Anomalous Endothermic Peak

ϕ_c, cooling rate. ○, griseofulvin; ○, proxyphylline; ●, chloramphenicol; △, spironolactone; ▲, brucine; □, acetaminophen; ■, nialamide

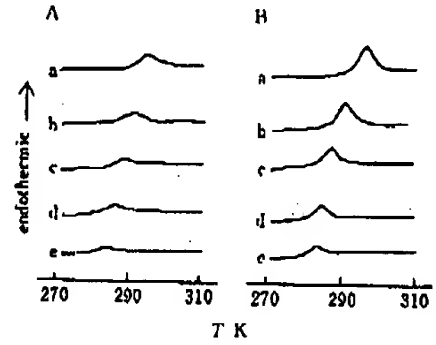

Fig. 4. Influence of Heating Rate on the DSC Curves of Glassy Tolnaftate Prepared at Two Different Cooling Rates

A, quenching; B, cooling rate of −1.25 K/min. Heating rate: a, 40; b, 20; c, 10; d, 5; e, 2.5 K/min.

the presence of an optimum temperature at which the area under the anomalous endothermic peak and T_g was maximum was recognized and could be explained by the relaxation theory.[5]

Thus, relaxation of the glass during preparation at various cooling rates was studied for 7 pharmaceuticals remaining stable at room temperature. The Intracooler I was used to cool the sample to 232 K. The melt was cooled to a specified temperature below T_g at various cooling rates, then heated to above T_g. Measurements were made at a heating rate of 40 K/min.

Figure 2 shows the DSC curves of glassy spironolactone and griseofulvin prepared at various cooling rates.

The T_g of glassy spironolactone varied from 331 K in the case of quenching to 333.5 K in the case of a cooling rate of −0.62 K/min.

The T_g of glassy griseofulvin varied from 370 to 373.6 K under these conditions. Thus, T_g increased and the area under the anomalous endothermic peak became larger with decrease in the cooling rate of the melts. Glassy spironolactone showed a broad anomalous endothermic peak, while glassy griseofulvin showed a sharp anomalous endothermic peak. The area under the anomalous endothermic peak of the DSC curve of glass prepared at each cooling rate and quenching are denoted by A and A_0, respectively. Then, to examine the rate and quantity of relaxation during cooling, A/A_0 was plotted against the logarithm of cooling rate. The results are shown in Fig. 3.

The samples were grouped into three classes by the rate

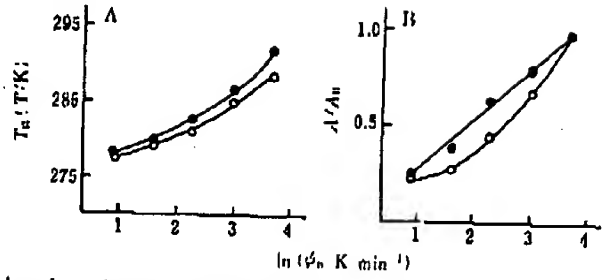

Fig. 5. Influence of Heating Rate on T_g and the Area under the Anomalous Endothermic Peak of Glassy Tolnaftate Prepared at Two Different Cooling Rates

A, T_g; B, A/A_0. ϕ_h, heating rate. ○, quenching. ●, cooling rate of −1.25 K·min.

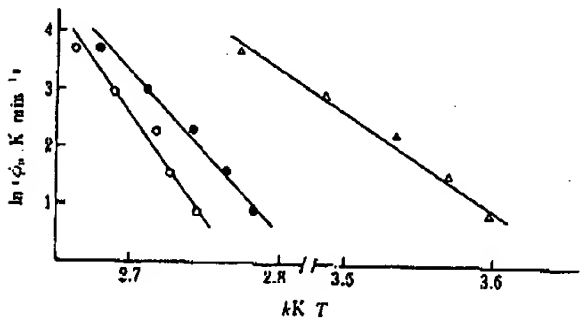

Fig. 6. Plots of $\ln \phi_h$ vs. $1/T_g$ of Glassy Chenodeoxycholic Acid, Griseofulvin and Tolnaftate Prepared at the Cooling Rate of −1.25 K/min

ϕ_h, heating rate. ○, chenodeoxycholic acid; ●, griseofulvin; △, tolnaftate.

and quantity of relaxation. Griseofulvin showed the most remarkable change in both factors, while acetaminophen and nialamide showed the smallest change. The effects of cooling rate during glass preparation on the anomalous endothermic peak of the glass formed varied with the samples. This indicates that a relaxation takes place during cooling in all 7 pharmaceuticals.

4) Influence of Heating Rate on Glass Transition The influence of heating rate of the glass on T_g was examined for three pharmaceutical samples: chenodeoxycholic acid had the largest T_g/T_m value of 0.85; griseofulvin had the highest T_m value of 497 K and with T_g nearly equal to that of chenodeoxycholic acid; and tolnaftate having comparatively low T_g value was examined as a sample with T_g/T_m nearly equal to that of griseofulvin. The influnce of heating rate of glassy tolnaftate prepared at two different cooling rates of −1.25 K/min and quenching on T_g and the area under the anomalous endothermic peak was examined. Measurements were made at heating rates ranging from 2.5 to 40 K/min.

Figure 4 shows the DSC curves of glassy tolnaftate prepared at a cooling rate of −1.25 K/min and quenching, respectively. The glass showed different DSC curves due to the structural relaxation during heating at different rates. The T_g decreased and the area under the anomalous endothermic peak became smaller with the decrease in the heating rate.

Figure 5 shows the influence of heating rate on T_g and the area under the anomalous endothermic peak of glassy tolnaftate prepared at two different cooling rates.

The area under the anomalous endothermic peak of the

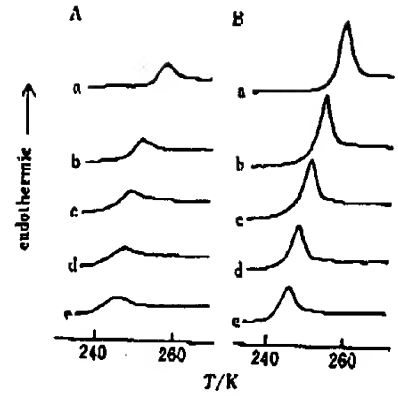

Fig. 7. Influence of Heating Rate of Glassy Aspirin Both Immediately and after Standing for 60 min at 232 K after Preparation of the Glass

A, 0 min; B, 60 min. Heating rate: a, 40; b, 20; c, 10; d, 5; e, 2.5 K/min.

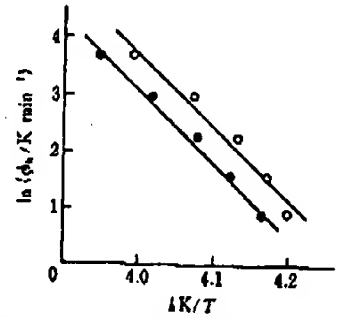

Fig. 8. Plots of $\ln \phi_h$ vs. $1/T_g$ of Glassay Aspirin

○, 0 min; ●, 60 min; ϕ_h, heating rate.

DSC curve of glass obtained at each heating rate and at the rate of 40 K/min are denoted by A and A_0, respectively. A/A_0 was plotted against the logarithm of the rate. The T_g and A/A_0 of both samples decreased as the heating rate decreased. Earlier studies on the effect of heating rate on T_g[3] revealed that T_g increased as the heating rate increased. From a logarithmic plot of the heating rate *vs.* $1/T_g$, the apparent activation energy of glass transition was calculated according to an equation derived by Barton.[6] Then, to compare two glassy pharmaceuticals with glassy tolnaftate, the influence of heating rate of glass prepared at the cooling rate of −1.25 K/min on T_g was examined.

A linear relationship was observed when the logarithm of the heating rate was plotted against $1/T_g$ (Fig. 6). The apparent activation energy of glass transition of chenodeoxycholic acid, griseofulvin and tolnaftate was calculated to be 273.6, 270.3 and 127.6 kJ/mol, respectively.

5) Influence of Isothermal Aging below T_g of Aspirin Aspirin exists as supercooled liquid at room temperature,[1] and was used as sample with low T_g of 243 K in examining the influence of isothermal aging below T_g on glass transition. After the melt was rapidly cooled to 232 K below T_g, the sample was kept at 232 K for 0 min or 60 min, then reheated to above T_g at various rates. Measurements were made at rates ranging from 2.5 to 40 K/min.

Figure 7 shows the influence of heating rate of glassy aspirin both immediately and after standing for 60 min at 232 K following preparation of the glass. The glass showed different DSC curves due to the structural relaxation during

continuous heating at different rates.

The T_g decreased and the area under the anomalous endothermic peak became smaller with decrease in the heating rate. Influence of heating rate on T_g was examined (Fig. 8).

A linear relationship was observed when the logarithm of the heating rate was plotted against $1/T_g$. The apparent activation energy of glass transition of both samples of aspirin was calculated as 105.6 kJ/mol.

Aspirin had the lowest T_g and T_g/T_m and the smallest apparent activation energy of glass transition, in contrast with chenodcoxycholic acid which had high T_g, the highest T_g/T_m and the largest apparent activation energy of glass transition examined in the present study.

References and Notes

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Appendix B

Advantages of Cyclic DSC (CDSC) over TMDSC

W.J. Sichina, National Marketing Manager

TMDSC (temperature modulated DSC) has many experimental pitfalls and problems associated with it due to the demands of the time-temperature sine wave coupled with the large mass furnace of the heat flux DSC instrument. For many samples, the sample response cannot keep up with the applied TMDSC sine wave. Experimental artifacts and erroneous data can then be obtained as a result of the inability of the heat flux DSC furnace and sample to respond adequately to the programmed sinusoidal temperature wave.

Because of the demands of the TMDSC approach in conjunction with a heat flux DSC, it is oftentimes necessary to use a very slow underlying heat ramp (2 C/min) with a long TMDSC period in order to obtain usable data. Even with 'simple' transitions, such as Tg, it has been found that the use of slow heating rates (i.e., 2 C/min) is necessary to properly study the Tg without the occurrence of artifacts. [References on this are S. Simon and G. McKenna, *NATAS Conference Proceedings*, 1998, Cleveland, p. 50-55 and S. Simon and G. McKenna, *NATAS Conference Proceedings*, 1997, Washington D.C., p. 358-365].

Because of the demands of TMDSC, it becomes time-consuming to study transitions, such as Tg. An alternative approach, which has the benefits of being more straightforward and less prone to experimental artifacts, is Cyclic DSC or CDSC. With the CDSC approach, a sample is heated quickly (i.e., 20 C/min) through its Tg, cooled at the same rate and then reheated at the same rate.

The first heat provides the 'as received' or *total heat flow* results on the sample. The second heat then yields the *reversible* aspects of the heat flow, such as the classic Tg without the occurrence of enthalpic relaxation. If the 2nd heat segment data are subtracted from the 1st heat, the *irreversible* aspects of the 'as received' sample will be obtained.

The reversible glass transition obtained in this manner is free from any hysteresis effects since the material was given a new and uniform thermal history by the CDSC approach. The material is cooled and heated through its Tg at the same rate (20 C/min), rendering it free from hysteresis effects. Thus, during the 2nd heating segment, a classic, stepwise change in the heat flow or heat capacity at Tg is obtained. This classic Tg is then easily analyzed.

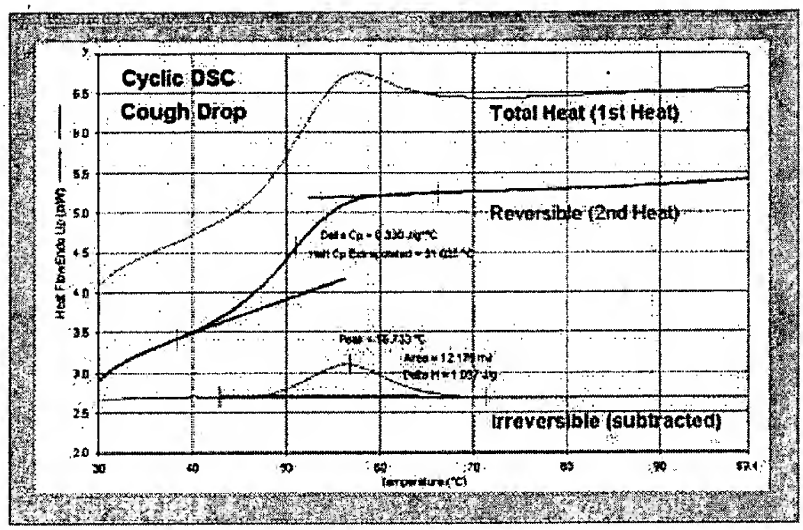
Displayed in the following figure are Cyclic DSC results generated using the PerkinElmer DSC 7. A cough drop, obtained from a pharmacy, was analyzed by heating the 'as received' sample at 20 C/min from 20 to 100 C, cooling at 20 C/min back to 20 C, and then reheating at 20 C/min from 20 to 100 C. The figure shows the 'as received' or total heat flow results, the reversible (2nd heat) signal and the irreversible component (subtracted data).

The CDSC results provide a clear identification of the physical events occurring at Tg for the cough drop. The 1st heat or total heat provides information on both chemistry as well as physics (thermal history) of the sample. The cough drop is primarily amorphous sugar and, as it sits on a store shelf, the amorphous material undergoes physical aging. This results in the occurrence of an enthalpic relaxation peak, or 'overshoot', at Tg.

When the cough drop is cooled and then reheated (at the same rate), a new and consistent thermal history is placed into the sample and loses its previous memory of physical aging. During the 2nd heating segment, the reversible aspects of the glass transition are obtained and a classic, stepwise change in the heat flow (without the overshoot peak) is observed.

If the 2nd heat results are subtracted from those of the 1st heat, the irreversible aspects of the aged cough drop sample can be simply extracted. The enthalpic relaxation peak is neatly obtained by the subtraction step and the magnitude of

PerkinElmer™ Instruments.



the peak is directly related to the aging time or temperature.

One main advantage of the CDSC approach over TMDSC is in timesaving. Since TMDSC is typically relegated to a heating rate of only 2 C/min, the time to heat a sample between 20 and 100 C would be 40 minutes. In comparison, a CDSC experiment conducted over the same temperature interval at a heating and cooling rate of 20 C/min would require only 14 minutes.

In addition to become more efficient from a time viewpoint, CDSC has the advantage of being much less prone to experimental artifacts. With TMDSC it is critical to ensure that the sample correctly follows the applied modulated input signal. The basic problem with the TMDSC heat flux DSC is that it utilizes a massive furnace and the large mass of the furnace coupled with the sample response yields numerous technical problems. This is why TMDSC is limited to very slow heating rates. It is essential that the underlying heating rate be slow enough and the TMDSC period be long enough to allow the sample response to keep up with the modulation and to provide an adequate number of modulation cycles through a given transition.

Summary

Cyclic DSC (CDSC) provides a straightforward means of extracting the following information from a material:

- Total heat flow or 'as received' properties
- Reversible
- Irreversible

In addition, CDSC offers the following advantages over TMDSC:

- Time savings due to use of fast heating and cooling rates (20 C/min versus 2 C/min)
- Ease of interpretation and experimental set-up
- Much less prone to experimental conditions as compared to TMDSC
- More accurate heat capacities
- Better resolution and sensitivity, especially with power compensated DSC

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